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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,980	10/28/2003	Thomas P. Jerussi	4821-528-999	3979

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EXAMINER	
SPIVACK, PHYLLIS G	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,980	JERUSSI, THOMAS P.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's Amendment filed May 25, 2006 is acknowledged. New claims 50 and 51 are presented. Accordingly, claims 41-51 are now under consideration.

The abstract of the disclosure was objected to in the last Office Action because the compounds, i.e., a racemic or optically pure sibutramine metabolite and an optional additional pharmacologically active compound, that are to be administered in the claimed methods, were not recited.

While it is noted the compounds of the present invention are now recited in the amended abstract, the present claims are not drawn to compositions. Accordingly, the objection of record is maintained.

In the last Office Action claim 49 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement with respect to a treatment modality of a prevention of depression wherein the "additional pharmacologically active compound" is an antimonic agent, a cardiovascular agent, an antiviral agent, an antibiotic, an antifungal or an antineoplastic.

The rejection of record under 35 U.S.C. 112, first paragraph, is withdrawn following the deletion of those additional pharmacologically active compounds that are recited above.

Claims 41-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention. The claims are directed to the treatment or prevention of depression comprising administering didesmethylsibutramine, (R)-

didesmethylsibutramine or (S)-didesmethylsibutramine. The specification provides no support for prevention of depression.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to prevention of depression. Given their broadest interpretation, according to The Merck Manual, the claims are drawn to methods of treating and preventing various disorders that involve diverse organ systems. See Table 189-1 on page 1527 and Table 189-2 on page 1529.

The relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the area of psychiatry or psychology.

Each particular type of depression has its own specific characteristics and etiology. The broad recitation "treating or preventing depression" is inclusive of many conditions that presently have only minimally successful therapies. A successful treatment modality for one particular type of depression, such as that which follows alcoholism, does not presage success for preventing another type of depression, as a neurological injury subsequent to stroke. Accordingly, the claims lack a credible asserted or well-established utility.

The breadth of the claims

The claims are very broad and inclusive of disorders of diverse etiology.

The amount of direction or guidance provided and the presence or absence of working examples

There are no working examples in which "(R)-didesmethylsibutramine and (S)-didesmethylsibutramine, is administered to prevent depression. No guidance is provided to prevent any type of depression. Such an assertion is clearly beyond the scope of the instantly claimed invention. The term "prevent" is an absolute definition that means to stop from occurring and thus requires a higher standard for enablement than does "therapeutic" or "treat". It is well established in the medical arts that the vast majority of diseases suffered by mankind cannot be totally prevented with current therapies.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to which particular compound would be preferred for preventing a particular type of depression that is encompassed in the claim language. The skilled artisan would expect the interaction of a particular compound in the prevention of a particular type of depression to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding. No direction is provided to distinguish therapy among the various types of depression or among the derivatives of didesmethylsibutramine that are disclosed in the specification. Absent reasonable *a priori* expectations of success for using a particular derivative to prevent any particular type of depression, one skilled in the psychology or psychiatric art would have to test extensively many conditions characterized by depression to discover which particular condition responds to a particular derivative. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

Considering the state of the art, as disclosed by the prior art of record, the high unpredictability of preventing depression and the lack of guidance provided by the specification, one of ordinary skill in the psychiatric art would be burdened with undue experimentation to prevent depression comprising administering the instantly claimed

compounds. Prevention entails the complete and absolute inhibition of the onset of depression and any manifestation thereof.

Applicant's arguments with respect to claims 41-49 that were rejected under 35 U.S.C. 103(a), as being unpatentable over Scott et al., British Journal of Pharmacology, in view of Jeffery et al., J. Chem. Soc. Perkin Trans., or Jacques et al., Wiley-Intersciences, NY, that was set forth in the last Office Action, has been considered but are moot in view of the new grounds of rejection.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 41-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young, J.W., WO 94/00047, or, Young, J.W., WO 94/00114, and Luscombe et al., Neuropharmacology.

Young teaches the administration of the optically pure (+) isomer of sibutramine in WO 94/00047 ('047) and the administration of the optically pure (-) isomer of sibutramine in WO 94/00114 ('114) to treat depression. See claim 1 in both documents. Further, Young teaches the importance of stereochemical purity in the field of pharmaceuticals where chirality is demonstrated. Some isomers may actually be deleterious while others are simply inert. Some are safe and effective while others are teratogenic. In the present case, Luscombe teaches metabolites of sibutramine (which is the tertiary amine), the secondary amine metabolite (BTS 54 354) and the primary

amine metabolite (BTS 54 505), which is didesmethylsibutramine, to be considerably more active than sibutramine. See Figure 1, page 129, and Table 1 on page 131. The references fail to teach optically pure enantiomers of didesmethylsibutramine. However, in view of the combined teachings of Young and Luscombe, one skilled in the art of formulation chemistry would have been motivated to prepare and administer an optically pure enantiomer of didesmethylsibutramine with a reasonable expectation of success in treating depression. Such would have been obvious in the absence of evidence to the contrary because Young teaches antidepressant activity following the administration of either optically pure (-) sibutramine or optically pure (+) sibutramine. Luscombe teaches the close structural relationship of sibutramine and its metabolite didesmethylsibutramine, as well as the demonstration of antidepressant activity of the active metabolite of sibutramine, didesmethylsibutramine. Because didesmethylsibutramine is also optically active, one skilled in the art would have been motivated to resolve the R(+)- and S(-) enantiomers through no more than routine experimentation and compare their efficacy in treating depression to the racemic didesmethylsibutramine. It would have been reasonable to expect such R(+)- and S(-) enantiomers would exhibit a lower side effect profile or an unexpected beneficial property.

The determination of both optimal dosage ranges and optimal modes of administration are parameters well within the purview of those skilled in the art through no more than routine experimentation.

The additional administration of drugs, as required by claims 48 and 49, such as selective serotonin reuptake inhibitors, serotonin modulators, hypnotics, sedatives, CNS stimulants, are well established in the prior art for the treatment of depression.

In the last Office Action claims 41, 46 and 47 were rejected under 35 U.S.C. 102(b) as being anticipated by Scott et al., British Journal of Pharmacology. It was asserted Scott teaches a method of treating depression comprising administering didesmethylsibutramine (BTS 54 505), a metabolite of sibutramine. Didesmethylsibutramine has a similar pharmacological profile to the parent compound *in vivo*; however, the metabolite is very much more potent than the parent compound. Claim 1 is not directed to the administration of an optical isomer of didesmethylsibutramine.

Applicant has not responded to this rejection of record under 35 U.S.C. 102(b). Accordingly, the rejection is maintained and presently extended to include claims 43-45 drawn to dosage ranges. Scott teaches the administration of a dosage range of 0.1-3.0 mg/kg. See column one, page 130 under *Prevention of reserpine-induced ptosis in rats*.

Claims 42 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

Claims 42 and 50 recite the limitations "(R)-didesmethylsibutramine and (S)-didesmethylsibutramine," respectively. There is insufficient antecedent basis for this limitation in independent claim 41 from which they depend.

Claims 41-51 are rejected under 35 U.S.C. 112, both first and second paragraphs, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and practice the invention, and, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention, with respect to the term "prodrug" in claim one.

Examples of prodrugs are disclosed in the specification on pages 3-5; however, the metes and bounds of the term cannot be precisely determined. The examples describe functional characteristics, such as biohydrolyzable moieties, without a clear recitation of those compounds contemplated. There is no showing of both preparation of such "prodrugs" or their utilization in the present methods of treatment of depression.

No claim is allowed.

Glick et al., European Journal of Pharmacology, is cited to show further the state of the art.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached from 10:30 to 7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 4, 2006

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER